SOFT TISSUE CALCIFICATIONS IN SYSTEMIC DISEASE*

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CALCIFICATION or ossification may occur in soft tissues secondary to local or systemic factors. Physiologic factors influencing normal and abnormal calcification include calcium and phosphorus ion concentration, alkaline phosphatase, tissue pH, vitamin D, hormonal balance or lack of it, blood supply and tissue injury.[1] Calcifications may be widespread or localized to a specific region or anatomic structure.

Metastatic calcification refers to tissue deposition of amorphous calcium phosphate and calcium hydroxyapatite crystals secondary to an increased serum calcium-phosphorous product. Microscopic calcification is common in the kidneys, lung, and stomach. Calcium salts may also be deposited diffusely in the soft tissues, blood vessels, or in intra or paraarticular locations.

Dystrophic calcification refers to the deposition of calcium salts in necrotic or dead tissue in patients with normal serum calcium and serum phosphorus levels. When dystrophic calcification occurs in the presence of osteoblastic activity it is known as ectopic calcification.[2] The pathophysiology of soft tissue calcification is not completely understood, but the location and appearance of the calcification may suggest the diagnosis. Table I presents a classification of soft tissue calcifications.

METASTATIC CALCIFICATION: HYPERCALCEMIA

Primary hyperparathyroidism. Primary and secondary hyperparathyroidism are frequently associated with soft tissue calcification. In primary hyperparathyroidism, elevation of serum calcium levels occurs, and in secondary hyperparathyroidism the serum phosphorus levels are frequently

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TABLE I. SOFT TISSUE CALCIFICATION

A) Metastatic calcification
- I) Hypercalcemia
  - a) Primary hyperparathyroidism
  - b) Milk alkali syndrome
  - c) Vitamin D intoxication
  - d) Miscellaneous
- II) Hyperphosphatemia
  - a) Secondary hyperparathyroidism
  - b) Tumoral calcinosis
  - c) Familial

B) Dystrophic calcification
- I) Collagen-vascular Disease
  - a) Scleroderma
  - b) Mixed connective tissue disease
  - c) Dermatomyositis
  - d) Systemic lupus erythematosis
- II) Metabolic disease
  - a) Crystal deposition disorders
    - 1) Gout
    - 2) Calcium pyrophosphate deposition disease
    - 3) Hydroxyapatite deposition disease
  - b) Miscellaneous
    - 1) Pseudo and pseudo pseudohypoparathyroidism
    - 2) Werner's syndrome
- III) Infestations
  - a) Cystercercosis
  - b) Loa loa
  - c) Dracunculosis
  - d) Leprosy
- IV) Vascular calcifications
  - a) Arterial
  - b) Venous
- V) Injection sites
  - a) Intramuscular injections
  - b) Calcium gluconate
- VI) Miscellaneous
  - a) Fat necrosis
  - b) Ehlers-Danlos syndrome
  - c) *Pseudoxanthoma elasticum*
- VII) Ectopic
  - a) Myositis ossificans progressiva
  - b) Myositis ossificans circumscripta
  - c) Following central nervous system trauma

elevated. A calcium-phosphorus product above 75mg./100ml. predisposes to metastatic calcification.

Intra-articular deposition of calcium pyrophosphate is not uncommon in patients with primary hyperparathyroidism, and crystals may be deposited

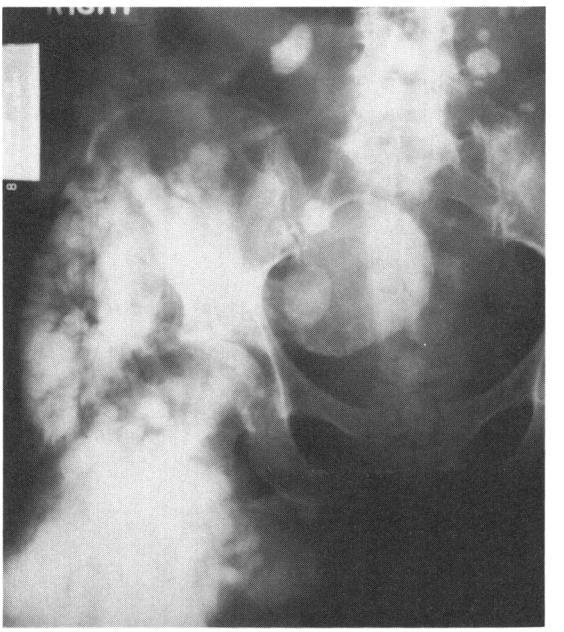

Fig. 1. Massive amorphous deposits of calcification about hip of patient with milk alkali syndrome

in hyaline or fibrocartilage. The calcium-phosphorus product in these patients may be completely normal. Calcium pyrophosphate deposition may be the commonest roentgen abnormality in patients with primary hyperparathyroidism.[3]

Primary hyperparathyroidism is found in 2 to 7% of patients with chondrocalcinosis,[4] and chondrocalcinosis has been reported in as many as 31% of patients with primary hyperparathyroidism.[3] When chondrocalcinosis occurs in multiple sites, particularly without associated joint disease, the diagnosis of hyperparathyroidism should be excluded.

Milk alkali syndrome. Milk alkali or "milk drinker syndrome" occurs in patients who consume large quantities of milk and alkali for peptic ulcer disease.[5] They may develop renal damage and eventually present with a fully developed syndrome of hypercalcemia without hypercalciuria or hypophosphatemia, calcinosis, and renal insufficiency.[5] The renal changes are irreversible but the soft tissue calcifications may disappear by lowering calcium intake, decreasing serum calcium levels.

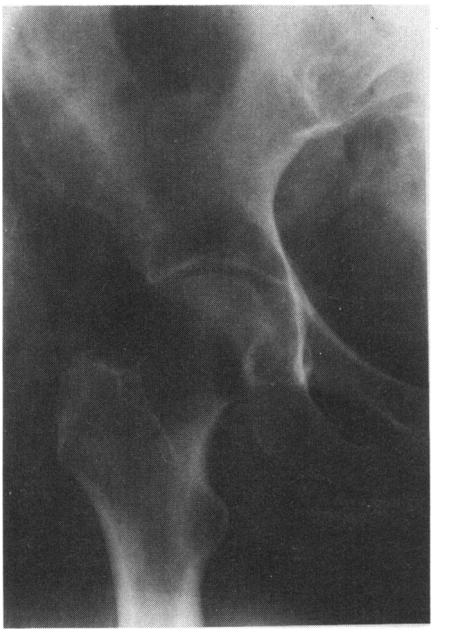

Fig. 2*a*. Soft tissue calcification in renal osteodystrophy. Anteroposterior view of right hip demonstrating para-articular soft tissue calcifications. Reproduced by permission from Desai, A., Eymontt, M., Alavi, A., et al.: Tc^{99m} MDP uptake in nonosseous lesions. *Radiology 135:*181-84, 1980.

Diffuse, amorphous deposits of calcium salts may be seen particularly in the subcutaneous and para-articular regions (see Figure 1).[6] The calcium deposits may vary in size and can erode intrinsically normal bone. Calcification may be widespread involving the falx, kidneys, lungs, and blood vessels.[6]

Vitamin D intoxication. Long-term massive intake of vitamin D may lead to hypercalcemia, soft tissue calcification, and renal insufficiency. Hypercalcemia secondary to massive vitamin D therapy may give rise to diffuse metastatic soft tissue calcification.[7,8] In children, periarticular and vascular calcifications may be associated with osteosclerosis.[7]

Miscellaneous. Other causes of hypercalcemia, including sarcoidosis,[9] Paget's disease, widespread malignancy, and multiple myeloma, may cause similar soft tissue calcification, but the hypercalcemia usually is corrected or the cause proves fatal prior to radiographic detection of calcification.

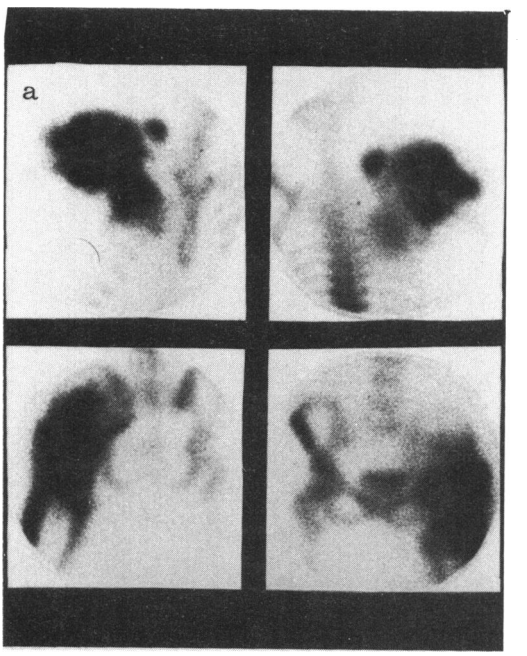

Fig. 2*b*. Bone scan of same patient revealing extensive calcification about hip and shoulder (a on left upper film is the anterior view). Reproduced by permission from Desai, A., Eymontt, M., Alavi, A., et al.: Tc^{99m} MDP uptake in nonosseous lesions. *Radiology 135:*181-84, 1980.

Increased Serum Phosphorus

Secondary hyperparathyroidism. Calcification in the extremities is more common in patients with secondary hyperparathyroidism with renal osteodystrophy than in those with primary hyperparathyroidism. Diffuse tumorlike masses in the soft tissues, primarily in para-articular locations, are not uncommon, particularly among dialysed patients. These calcifications may be extensive or relatively subtle; bone scanning is particularly helpful in the latter (see Figure 2).[10] These diffuse metastatic soft tissue calcifications may disappear following correction of the metabolic abnormality.[11]

Patients with secondary hyperparathyroidism may have diffuse arterial calcification which may be extensive (Figure 3). This increases with the age of the patient and time on dialysis and does not correlate with the presence of bone disease.[12] Extensive small vessel calcification may be complicated by occlusion and gangrene.[13] Progression of soft tissue calcification following renal transplantation is evidence of advancing secondary

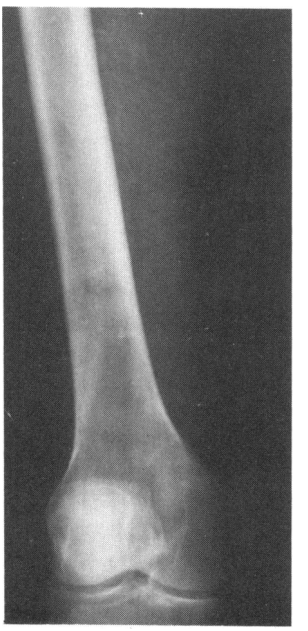

Fig. 3. Extensive vascular calcification in patient with renal osteodystrophy

hyperparathyroidism,[14] and may be an indication for subtotal parathyroidectomy, even in the absence of osseous abnormalities.[14]

Patients with chronic renal disease may have associated crystal deposition disorders. The deposition of monosodium urate, calcium pyrophosphate, and hydroxyapatite crystals may cause acute symptoms. These will be discussed with the crystal deposition disorders.

Tumoral calcinosis: Tumoral calcinosis is a poorly defined entity frequently associated with increased serum phosphorus levels. Tumoral calcinosis is familial in approximately a third of cases and is more common among blacks.[15] Such tumors usually present as a painless mass or masses during the first and second decades of life.[16] Radiologically, large amorphous calcific deposits are present, frequently about the large joints (Figure 4). These tumoral masses may layer on erect filming.[17,18] The masses may cause bony erosion, and the incidence of postsurgical recurrence is high.

Many of the reported patients with tumoral calcinosis have been inadequately studied and a suggested error in phosphorus metabolism may be more prevalent than stated, but the primary defect may be in the collagen-

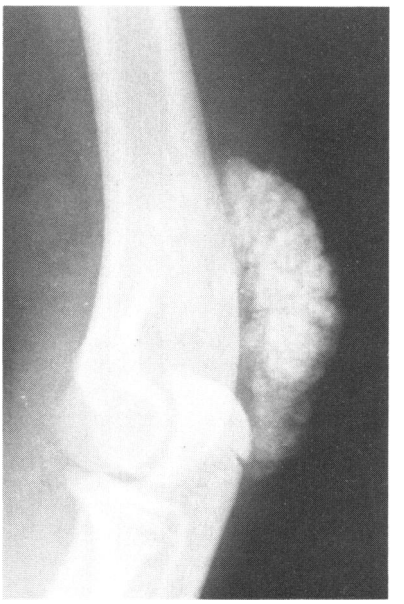

Fig. 4. Large calcific mass about elbow of patient with tumoral calcinosis. Reproduced by permission from Desai, A., Eymontt, M., Alavi, A., et al.: Tc^{99m} MDP uptake in nonosseous lesions. *Radiology 135:*181-84, 1980.

ous tissue which calcifies, rather than an error in phosphorus metabolism.[19]

Familial increase in serum phosphorus. We have seen a patient with normal renal function, normal serum calcium levels, normal parathyroid function, and increased serum phosphorus levels who had diffuse soft tissue calcifications, mainly in the lower extremities. Vascular and paraarticular calcification was also present. The patient had a sister with the same biochemical and radiologic abnormalities.

Metastatic calcification from any cause may be "tumoral" or "diffuse" as well as intra- or para-articular. The location and morphologic appearance of metastatic calcification represent nonspecific responses to the increased serum calcium-phosphorus product. Amorphous calcific deposits identical to those seen in tumoral calcinosis may occur with secondary hyperparathyroidism or the milk alkali syndrome, even with layering in the erect position. Our patient with increased serum phosphorus levels presented with diffuse soft tissue calcification, while increased serum phosphorus levels are common in tumoral calcinosis.

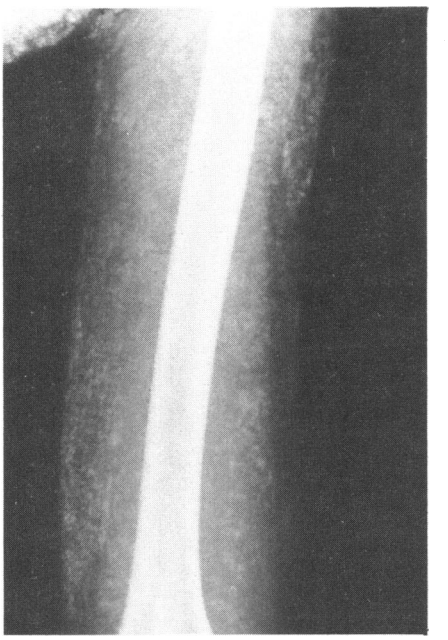

Fig. 5. Extensive deposition of calcium in subcutaneous tissue, muscle and interfascial planes of patient with dermatomyositis

Dystrophic Calcification

Collagen vascular disease. Soft tissue calcifications are common in patients with collagen vascular diseases, particularly scleroderma, mixed connective tissue disorder, dermatomyositis, and systemic lupus erythematosis. The soft tissue calcification occurs in areas of tissue necrosis and hence is dystrophic.[20]

The distribution of soft tissue calcification in collagen vascular diseases occurs in two major patterns which may occur idependently or in combination. *Calcinosis circumscripta* refers to well defined, localized calcium deposits, most commonly seen in the upper extremities, particularly about the terminal phalangeal tufts. Calcinosis circumscripta is more common in women and its presence suggests the diagnosis of scleroderma or mixed connective tissue disease. Occasionally, intra-articular calcinosis and joint erosions may occur with calcinosis circumscripta.[21] *Calcinosis universalis* refers to sheetlike deposits of calcification in subcutaneous tissue, muscle, and interfascial planes. This type of calcification is most common in the proximal limb muscles and suggests a collagen vascular disorder, usually dermatomyositis (Figure 5).

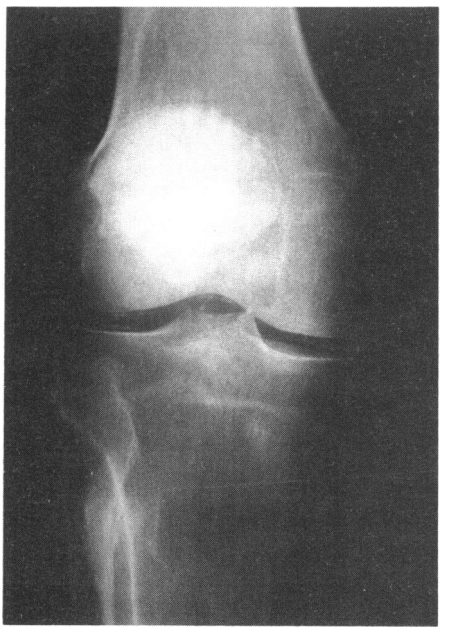

Fig. 6*a*. Chondrocalcinosis. Posterior-anterior view of knee

Calcinosis is very common in patients with childhood dermatomyositis, particularly that affecting subcutaneous tissues. When extensive interfascial calcification occurs it is usually in patients with severe disease and subcutaneous calcification.[22] This calcification may be associated with ulceration of the overlying skin and may regress without treatment.[22] Calcification occurs four months to 12 years following the onset of the disease.[22] Radiologically, soft tissue edema secondary to muscular inflammation occurs before the soft tissue calcification. Continued muscle necrosis leads to calcification and ossification, frequently associated with musmuscular atrophy, fibrosis, and joint contractures.[23]

Budin and Feldman reported eight patients with systemic lupus erythematosis and soft tissue calcification.[24] Two patients had arterial calcification without other predisposing causes. One of their patients had associated diffuse soft tissue calcification. Weissman et al. stated that periarticular soft tissue calcifications in the hands and terminal tuft resorption in patients with systemic lupus erythematosus is associated with Raynaud's phenomena.[25]

Some patients manifest features of more than one connective tissue

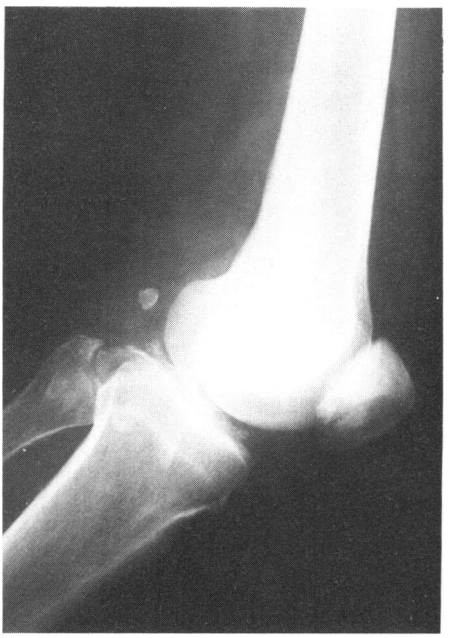

Fig. 6*b*. Lateral view of knee in same patient with extensive calcification of the menisci and articular cartilage

disorder. These patients can be divided into two groups. Patients with a high antibody titer to the ribonuclear component of extractable nuclear antigen (ENA), and particularly to RNA sensitive nuclear extractable antigen (NEA), are considered to have mixed connective tissue disorder.[26,27] Patients with overlapping features of more than one collagen vascular disease without antigen abnormalities are referred to as having "overlap syndromes."[26] Small intra-articular erosions and soft tissue calcifications are common to both these syndromes, as are gastrointestinal and pulmonary abnormalities.[26,27] Mixed connective tissue disorder has a relatively good prognosis because renal disease is uncommon and the response to steroids is usually predictable.[27]

Metabolic Diseases

Crystal deposition disorders. The crystal deposition disorders include gout, pseudogout, and hydroxyapatite deposition disease. Any of these disorders may occur as primary abnormalities or secondary to other disease states.

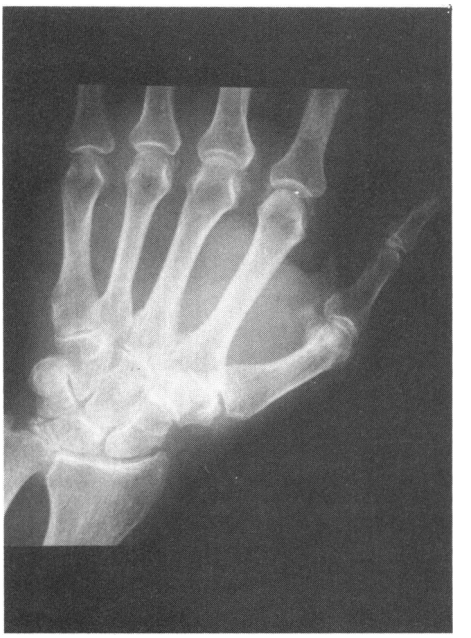

Fig. 7. Calcification in the triangular fibrocartilage of the wrist. Calcification is also identified about the meta carpal phalangeal joints of the 2-4th digits and in the articular cartilage of the radius and navicular

Gout. Gout is characterized by the deposition of monosodium urate crystals in soft tissues and joints. Patients frequently present with acute arthritis at a first metatarsal phalangeal joint, associated with hyperuricemia, which responds rapidly to colchicine. In patients with a less typical presentation, the diagnosis can be established by demonstrating monosodium urate crystals inside the leukocytes of synovial fluid or in tophacious deposits.

Gout may be primary, occurring as an idiopathic abnormality or as an inherited trait. It may also occur secondary to acquired hyperuricemia and often occurs among patients with hematologic disorders, renal disease, drug therapy, or hypertensive cardiovascular disease. Gout is frequently an asymmetric, polyarticular disease and rarely involves the axial skeleton. Bony erosions with "overhanging edges,"[28] asymmetry, and lack of osteoporosis should suggest a diagnosis of gout. Soft tissue swellings or tophi may contain amorphous calcific deposits, but these suggestive and characteristic radiologic findings do not occur until late in the course of the disease.

TABLE II. CALCIUM PYROPHOSPHATE DEPOSITION DISEASE

A) Metabolic disorders
   1) Primary hyperparathyroidism
   2) Wilson's disease — hepatolenticular degeneration
   3) Hemachromatosis
   4) Acromegaly
   5) Ochronosis
   6) Hypophosphatasia
B) Familial
C) Idiopathic (pseudogout)
D) Miscellaneous
   a) Age
   b) Gout
   c) Collagen vascular disease
   d) Hemophilia
   e) Osteoarthritis?

Calcium pyrophosphate deposition disease (CPPD) is characterized by the presence of calcium pyrophosphate crystals in synovial fluid, cartilage, and soft tissues. These patients may present with an acute or chronic arthritis simulating gout, but the diagnosis may be suspected radiologically when one sees intra-articular, frequently symmetrical calcification within the fibrocartilage, hyaline cartilage, and joint capsule.[4] Hyaline cartilage calcification tends to be linear, while calcification of fibrocartilage tends to have a punctate pattern. Examination of synovial fluid crystals under polarized light microscopy reveals weakly positive birefringence, whereas monosodium urate crystals show strongly negative birefringence.[29]

The arthropathy of calcium pyrophosphate deposition disease may occur with or without chrondrocalcinosis.[30] When hands and wrists are involved there is a tendency for radial carpal and metacarpal phalangeal involvement.[30,31] Joint changes simulate osteoarthritis with joint space narrowing, subchondral eburnation, and cyst formation. The knees are the most commonly involved joint (Figure 6), followed by the wrist (Figure 7) and metacarpal phalangeal joints. In the knees, patellar femoral joint involvement is frequently out of proportion to the changes in the medial and lateral joint compartments.[31]

Patients with calcium pyrophosphate deposition disease may be asymptomatic or present with an arthritic syndrome simulating gout. The syndrome of acute joint pain associated with calcium pyrophosphate crystals in the synovial fluid is known as the pseudogout syndrome. This may be associated with a large number of diseases (Table II), but when it is idiopathic it is called pseudogout.

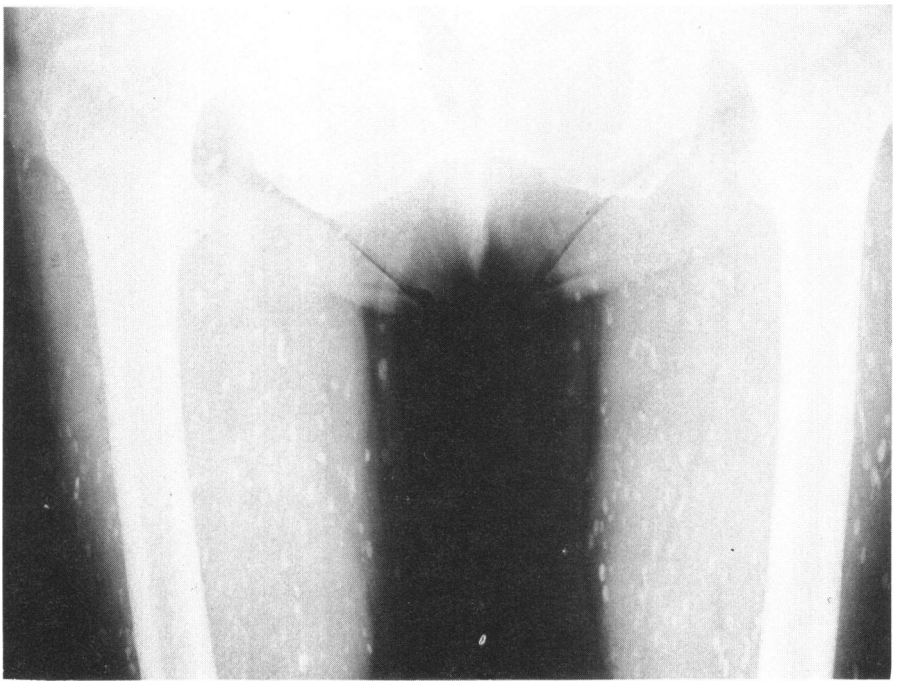

Fig. 8*a*. Cystercercosis. Anteroposterior view of both proximal femurs demonstrating rod-shaped, fusiform calcifications in the soft tissues running parallel to the muscle fibers

Hydroxyapatite deposition disease (HADD). Deposition of hydroxyapatite crystals may cause acute pain and inflammation, usually in a periarticular region, which frequently leads to monoarticular periarthritis. Hydroxyapatite deposition disease, however, may occur in multiple intra- and para-articular sites,[32] and the crystals may precipitate acute symptoms. The disease may exist as a primary para-articular disease, may involve multiple sites, and can cause joint destruction. It has been described in patients with scleroderma,[33] mixed connective tissue disorder,[34] and in patients receiving chronic hemodialysis.[35]

The definitive diagnosis of hydroxyapatite-induced arthritis can only be made by x-ray defraction analysis or electron microscopic demonstration of crystals.[36] Homogeneous periarticular calcifications adjacent to tendinous insertions strongly suggest hydroxyapatite deposition disease. This is most commonly seen about the shoulder, hip, elbow, wrist, and knee. Amorphous intra-articular calcifications should also raise this possibility.

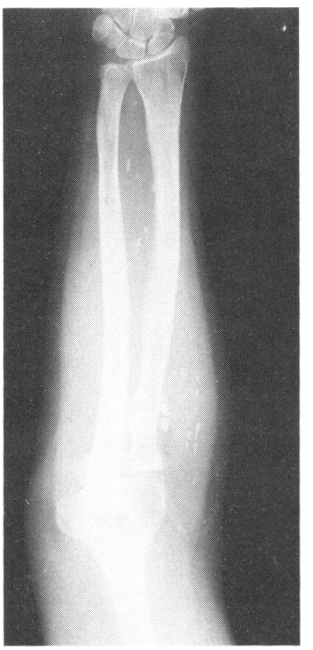

Fig. 8*b*. Anteroposterior of forearm in same patient revealing similar rod-shaped calcifications typical of cystercercosis

Pseudo and pseudopseudo hypoparathyroidism. Pseudo and pseudopseudo hypoparathyroidism have a characteristic phenotype consisting of short stature, brachydactylia, round facies, and short, broad nails. Patients with pseudohypoparathyroidism have low serum calcium and high serum phosphorus levels. They fail to respond normally to parathyroid hormone. Patients with pseudo pseudohypoparathyroidism have normal serum calcium and phosphorus levels. Cataracts, mental retardation, and defective teeth occur in both entities.[37,38] The two syndromes overlap considerably; calcium levels may vary within the same patient and members of the same family may have either of the two abnormalities. These syndromes may represent different manifestations of the same genetic entity.[39,40]

Short metacarpals and metatarsals, particularly the fourth and fifth rays, and calcifications in the soft tissue and basal ganglia are common. The soft tissue calcifications are small and often involve periarticular regions.[41] Nodules may be present in the scalp and extremities,[41] and the calvarium is frequently thickened. Patients with pseudo pseudohypoparathyroidism may develop hyperparathyroidism, presumably secondary to stimulation of the

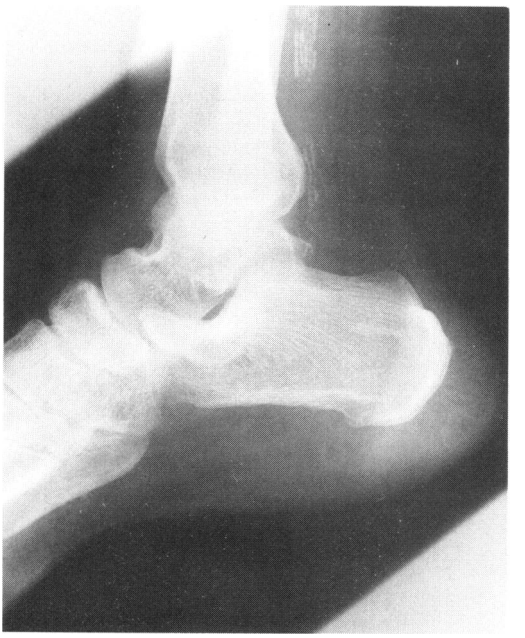

Fig. 9*a*. Leprosy. Calcification in the sural nerve

parathyroid glands by low serum calcium levels.[41]

Werner's syndrome. Werner's syndrome consists of premature aging, which usually starts in adolescence, cataracts, and changes in the skin simulating scleroderma. The patients are frequently short in stature. Endocrine abnormalities, including diabetes mellitus and hypogonadism, are frequent. This syndrome is associated with a high incidence of heart disease and cancer.[42]

Radiologically, generalized osteoporosis with soft tissue and muscular atrophy is common, and is frequently associated with skin ulcers and subcutaneous and peripheral arterial calcifications. An unusual, erosive noncharacteristic arthritis has been described,[42,43] as have gross foot deformities with frank osteomyelitis.[42] Many of the cases reported have occurred in people of Jewish[42] and Japanese[44] descent.

INFESTATION

Soft tissue calcifications have been described secondary to infestation by various parasites.

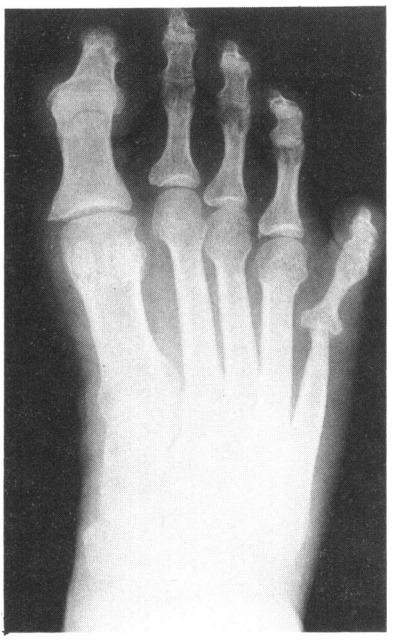

Fig. 9*b*. Foot of same patient demonstrating narrowing of the distal fifth metatarsal shaft, a neuropathic change of leprosy

Cystercercosis is acquired by ingestion of the pork tapeworm, *Taenia solium*. Calcification usually occurs about 10 years following the initial infestation and may be an incidental radiologic finding. Calcifications—fusiform in appearance, and approximately 3 mm. in size and parallel to the muscle fibers (Figure 8)[45]—occur in muscle and brain.

Loiasis is caused by the loa loa or African eye worm. The disease is endemic in many parts of West Africa and in the equatorial rain forest.[45] Painful pruritic subcutaneous swellings frequently occur in the hands, forearm, and orbit. These last three to five days and may cause temporary visual problems. The worms may live in the subcutaneous tissue and migrate before death.[45] The dead worms can cause abscesses or undergo calcification, particularly in the hands and feet.[45] The parasites appear in roentgenograms as fine, lacelike calcifications several millimeters in length.[45] Thicker densities with lobulated contours have been described, and may represent calcification in the fibrous capsules surrounding the worm.[45]

Dracunculosis. *Dracunculosis mediensis*, the guinea worm, is ingested in

its larval form with contaminated drinking water, and penetrates the wall of the digestive tract and matures in the retroperitoneum. Females migrate through the soft tissues of the trunk and extremities, but the fate of male worms is unknown.[45] The parasite penetrates the surface of the skin, preferring areas in contact with moisture into which it can discharge larvae. Symptoms may be secondary to local inflammation or have an allergic basis.[45]

A guinea worm may calcify after death and appear as a long, thin streak in roentgenograms. The female may reach a length of 100 cm. and extend throughout most of the length of the lower extremity. The worm may undergo calcification in a coiled position and give rise to an appearance of heterogeneous masses of small particles, the "chain mail" configuration.[45]

Leprosy may cause calcification in peripheral nerves (Figure 9*a*), most commonly the sural and greater auricular nerves, which may be palpable. Nerve calcification is frequently associated with other radiologic manifestations of the disease. (Figure 9*b*)[45]

Vascular Calcifications

Arterial. Arterial calcifications may occur in the media or intima. Calcification in the media is known as Monckeberg's arteriosclerosis. It usually occurs in large muscular arteries and, when present before the age of 50, raises the possibility of diabetes mellitus or chronic renal disease. Moskowitz, in a double blind study of patients over 60, found that 22 of 23 patients with Monckeberg's sclerosis had diabetes mellitus.[46] Monckeberg's arteriosclerosis does not cause lumino-occlusive disease, and is thought to have a benign course.[46] The entire vessel is circumferentially involved by a fine grain, diffusely distributed calcification.[46]

Calcification in the intima is plaquelike, irregular, and causes liminal narrowing and decreased blood flow. The presence of intimal calcification may suggest coronary artery calcification.

Venous. Venous calcification may occur as phleboliths, calcified thrombi, or calcification in the wall of veins.[7] Phleboliths present radiographically as ringlike calcifications with lucent centers. Common in the pelvis, they may be seen in the extremities. Calcified phleboliths may also occur in arterial venous malformations. Phleboliths are thought to represent calcified thrombi densely adherent to the intima.[7]

Long, calcified thrombi and calcification in venous walls are uncommon in peripheral veins. Patients with severe venous stasis may develop

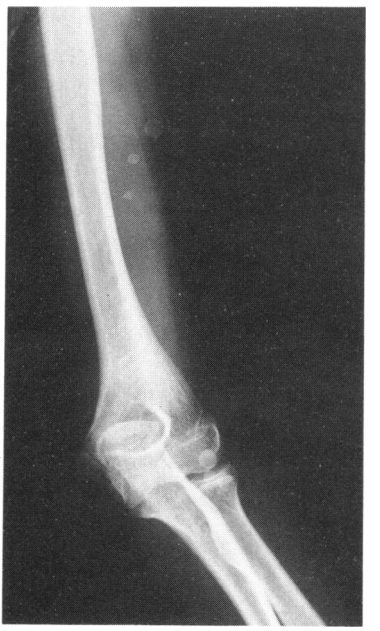

Fig. 10*a*. Ehlers-Danlos syndrome. Arm of patient demonstrating ring-like calcifications resembling phleboliths

extensive subcutaneous calcification and ossification which is frequently associated with periostitis and phleboliths.[47]

Intramuscular Injection Sites

Calcifications may occur in soft tissues following local intramuscular injections. In the buttocks and thighs they frequently have a ringlike radiographic configuration and resemble phleboliths. In the deltoid muscle the calcifications may be solid.[48] These soft tissue calcifications are thought to be secondary to local hemorrhage. They are unrelated to the type of medication and are of no clinical significance.[48]

Calcification may occur following intramuscular or intravenous injection of calcium gluconate.[49,50] This form of calcification is common in subcutaneous tissues and may also be identified in vessels.[49,50] The calcifications seen in radiographs is not the injected calcium gluconate but calcification within necrotic soft tissues at the injection site. The calcification takes approximately two weeks to appear and usually resolves in about six weeks.[49]

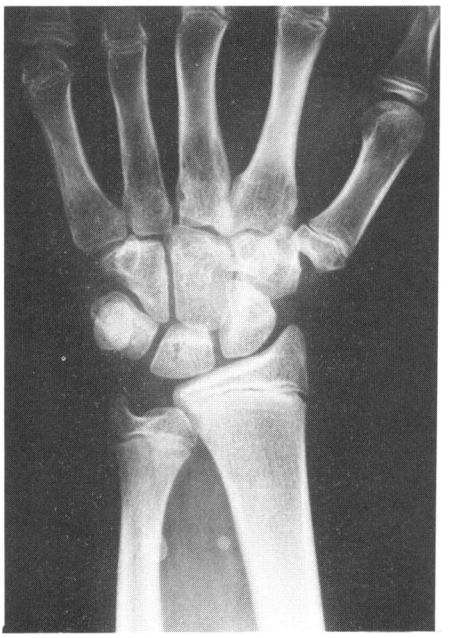

Fig. 10*b*. Wrist of same patient showing two smaller calcified lesions between the radius and ulna

MISCELLANEOUS

Fat necrosis. Calcification secondary to fat necrosis is usually discovered shortly after birth and may occur during the neonatal period. Its etiology is unknown but it has been reported in infants of diabetic mothers and following obstetrical trauma, hypothermia,[51] and in association with infantile hypercalcemia. The overlying skin frequently has a violaceous hue, and the subcutaneous tissue demonstrates well-circumscribed, slightly raised firm areas. Lesions may be few or widespread, and the calcification is usually resorbed within a period of weeks or months. The distribution of the soft tissue calcification is relatively symmetrical, and associated necrosis of the visceral fat is uncommon.[52]

Ehlers Danlos syndrome is a familial connective tissue disorder with a dominant Mendelian inheritance characterized clinically by hyperextensibility of the skin and joints. Pes planus, genu recurvatum, and dislocations are frequent and osteoarthritis is commonly found in adults.[53,54]

Radiologically calcified subcutaneous speroids occurred in 29 of 100 patients in the series reported by Beighton and Thomas.[54] These were

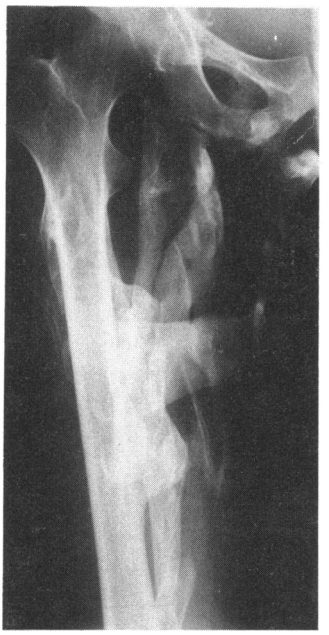

Fig. 11. Extensive ossification of soft tissues about femur in patient with myositis ossificans progressiva

most common over the bony prominence of the extensor surfaces, vary in size between 2 and 10 mm., and may resemble phleboliths (Figure 10).[53-55] Nodules represent lobules of calcified necrotic fat surrounded by dense fibrous tissue capsules and may represent a response to repeated trauma.[55] Diverticula of the gastrointestinal tract and kyphoscoliosis are frequent with this syndrome.[54]

Pseudoxanthoma elasticum is characterized by degeneration of elastic fibers and soft tissue calcifications. It is inherited as an autosomal recessive trait. Histologically, calcifications occur in the elastic tissue[56] and in the middle and deep dermal layers of the skin.[57] Vascular calcification characteristically occurs in the media of large arteries, most commonly the femoral vessels.[58] Juxta-articular calcifications occur in the elbows, hips and interphalangeal joints.[57]

The disease may involve the skin, where it leads to a loss of elasticity and yellowish papules with a cobblestone appearance, mainly on the flexor surfaces. Angiod streaks may be identified in the retina, and retinal hemorrhage can lead to blindness. Changes in elastic tissue may lead to

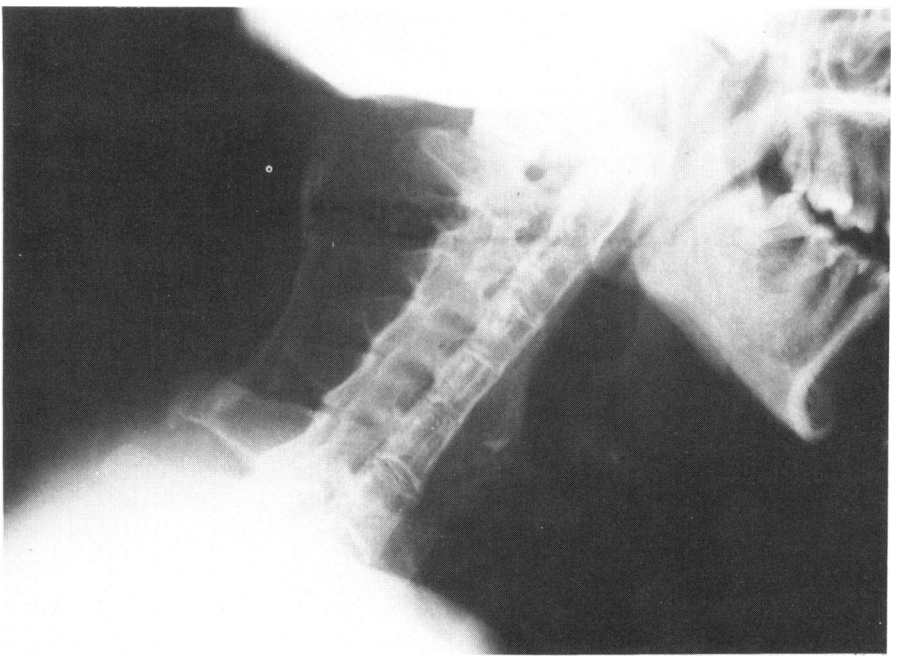

Fig. 12. Myositis ossificans progressiva with soft tissue ossification, fusion of the hypoplastic bodies of the cervical spine, and calcification in the intervertebral disc cartilages

changes in the blood vessels and cause gastrointestinal hemorrhage, ischemia, hypertension, or intermittent claudication.[57,58]

Ectopic Calcification

Myositis ossificans progressiva is characterized by progressive extraskeletal ossification associated with abnormalities of the first toe and thumb.[59] Recently the term "fibrodysplasia ossificans progressiva" has been suggested because connective tissues are involved primarily and the muscular involvement is secondary.[60] Microdactylia or adactylia of the great toes and thumbs should suggest a diagnosis prior to clinical presentation. The disease usually starts in early life and is progressive. Patients frequently complain of tender soft tissue swellings which remit and exacerbate, often in relation to minor trauma.[60] In addition to extensive ossification of the soft tissues (Figure 11), one may see fusion of the cervical spine with calcification of intervertebral discs (Figure 12).

Myositis ossificans circumscripta: Myositis ossificans may occur in a local area with or without a history of trauma, and this form is referred to as pseudomalignant osseous tumor of soft tissue.[61,62] These patients present with a tender soft tissue mass. Histologically, lesions demonstrate centrifugal or zonal maturation with a cellular center and immature osteoid at the periphery.[63,64] A radiolucency usually separates the lesion from underlying normal bone.

Central nervous system following trauma. Ectopic ossification is a process in which new bone formation occurs in tissues which normally do not ossify.[2] The histologic appearance of this new bone is identical to post-traumatic myositis ossificans. Ossification in such patients usually occurs about the large joints, particularly the hip or knee, where they may mimic acute arthritis.[65] Extra-articular bony ankylosis occurs in three to 8% of patients.[65] There is no relationship between the sex of the patient and level of spinal cord injury and the incidence of ectopic bone formation, but ectopic bone formation is more frequent in patients with complete paralysis.[66] This heterotopic ossification may also follow closed head injury[67] or burns.[68] Following burns, calcification frequently occurs in upper limbs and often resolves spontaneously.[13]

REFERENCES

1. Dalinka, M. K., Lally, J. F., Azimi, F., and Gingerilli, F.: Calcification in undifferentiated abdominal malignancies. *Clin. Radiol. 26:*115-19, 1975.
2. Kewalramani, L. S.: Ectopic ossification. *Am. J. Phys. 56:*99-121, 1977.
3. Rynes, R. I. and Merzig, E. G.: Calcium pyrophosphate crystal deposition disease and hyperparathyroidism: A controlled, prospective study. *J. Rheum. 5:*460-68, 1978.
4. Genant, H. K.: Roentgenographic aspects of calcium pyrophosphate dihydrate crystal deposition disease (pseudogout). *Arthritis Rheum. 19:*307-28, 1976.
5. Burnett, C. H., Commons, B. R., Albright, F., and Howard, J. E.: Hypercalcemia without hypercalcuria or hypophosphatemia, calcinosis and renal insufficiency. A syndrome following prolonged intake of milk and alkali. *N. Engl. J. Med. 240:*787-94, 1949.
6. Poppel, M. H.: Roentgen manifestations of milk drinker's syndrome. *Radiology 67:*195-99, 1956.
7. Gayler, B. W. and Brogdon, B. G.: Soft tissue calcifications in the extremities in systemic disease. *Am. J. Med. Sci. 249:*130-45, 1965.
8. Danowski, T. S., Winkler, A. W., and Peters, J. P.: Tissue calcification and renal failure produced by massive dose vitamin D therapy of arthritis. *Ann. Intern. Med. 23:*22-29, 1945.
9. Lathan, S. R., Block, R. A., and McLean, R. L.: Sarcoidosis with metastatic calcification. *Am. J. Med. 44:*1000-04, 1968.
10. Desai, A., Eymontt, M., Alavi, A., Schaffer, B., and Dalinka, M.: Tc^{99m} MDP Uptake in Nonosseous Lesions. *Radiology 135:*181-84, 1980.
11. Alfrey, A. C., Jenkins, D., Groth, C. G., et al.: Resolution of hyperparathyroidism, renal osteodystrophy and metastatic calcification after renal homotransplantation. *N. Engl. J. Med.*

*279:*1349-56, 1968.
12. Meema, H. E., Oreopoulos, D. G., and deVeber, G. A.: Arterial calcifications in severe chronic renal disease and their relationship to dialysis treatment, renal transplant, and parathyroidectomy. *Radiology 121:*315-21, 1976.
13. Friedman, S. A., Novack, S., and Thomson G. E.: Arterial calcification and gangrene in uremia. *N. Engl. J. Med. 280:*1392-94, 1969.
14. Peterson, R.: Small vessel calcification and its relationship to secondary hyperparathyroidism in the renal homotransplant patient. *Radiology 126:*627-33, 1978.
15. Longacre, A. M. and Sheer, A. L.: Tumoral calcinosis. Case presentation and review of 55 cases in the literature. *J. Florida Med. Assoc. 61:*221-25, 1974.
16. Palmer, P. E. S.: Tumoural calcinosis. *Br. J. Radiol 39:*518-25, 1966.
17. Kolawole, T. M. and Bohrer, S. P.: Tumoral calcinosis with "fluid levels" in the tumoral masses. *Am. J. Radiol. 120:*461-65, 1974.
18. Hug, I. and Guncaga, J.: Tumoral calcinosis with sedimentation sign. *Br. J. Radiol. 47:*734-36, 1974.
19. Hacihanefioglu, U.: Tumoral calcinosis. A clinical and pathological study of eleven unreported cases in Turkey. *J. Bone Joint Surg. 60A:*1131-36, 1978.
20. Steiner, R. M., Glassman, L., Schwartz, M. W., and Vanace, P.: The radiological findings in dermatomyositis of childhood. *Radiology 111:*385-93, 1974.
21. Brower, A. C., Resnick, D., Karlin, C., and Piper, S.: Unusual articular changes of the hand in scleroderma. *Skeletal Radiol. 4:*119-23, 1979.
22. Sewell, J. R., Liyanage, B., and Ansell, B. M.: Calcinosis in juvenile dermatomyositis. *Skeletal Radiol. 3:*137-43, 1978.
23. Ozonoff, M. B. and Flynn, F. J.: Roentgenologic features of dermatomyositis of childhood. *Am. J. Radiol. 118:*206-12, 1973.
24. Budin, J. A. and Feldman, F.: Soft tissue calcifications in systemic lupus erythematosus. *Am. J. Radiol. 124:*358-64, 1975.
25. Weissman, B. N., Rappoport, A. S., Sosman, J. L., and Schur, P. H.: Radiographic findings in the hands in patients with systemic lupus erythematosus. *Radiology 126:*313-17, 1978.
26. Silver, T. M., Farber, S. J., Bole, G. G., and Martel, W.: Radiological features of mixed connective tissue disease and sclerodermasystemic lupus erythematosus overlap. *Radiology 120:*269-75, 1976.
27. Udoff, E. J., Genant, H. K., Kozin, F., and Ginsberg, M.: Mixed connective tissue disease: The spectrum of radiographic manifestations. *Radiology 124:* 613-18, 1977.
28. Martel, W.: The overhanging margin of bone: A roentgenologic manifestation of gout. *Radiology 91:*755-56, 1968.
29. McCarty, D. J. and Haskin, M. E.: The roentgenographic aspects of pseudogout (articular chondrocalcinosis): An analysis of 20 cases. *Am. J. Radiol. 90:*1248-57, 1963.
30. Resnick, D. and Utsinger, P. D.: The wrist arthropathy of "pseudogout" occurring with and without chondrocalcinosis. *Radiology 113:*633-41, 1974.
31. Resnick, D., Niwayama, G., Goergen, T. G., et al.: Clinical, radiographic and pathologic abnormalities in calcium pyrophosphate dihydrate deposition disease (CPPD): Pseudogout. *Radiology 122:*1-15, 1977.
32. Bonavita, J. A., Dalinka, M. K., and Schumacher, H. R.: Hydroxyapatite deposition disease. *Radiology 134:*621-25, 1980.
33. Resnick, D., Scavulli, J. F., Goergen, T. G., et al.: Intra-articular calcification in scleroderma. *Radiology 124:*685-88, 1977.
34. Reginato, A. J. and Schumacher, H. R.: Synovial calcification in a patient with collagen-vascular disease: Light and electron microscopic studies. *Am. J. Radiol. 4:*261-71, 1977.
35. Thompson, G. R., Ting, Y. M., and Riggs, G. A.: Calcific tendonitis and soft tissue calcification resembling gout. *J.A.M.A. 203:*464-72, 1968.
36. Schumacher, H. R., Somlyo, A. P., Tse, R. L., and Maurer, K.: Arthritis

associated with apatite crystals. *Ann. Intern. Med. 87:*411-16, 1977.
37. Arnstein, A. R., Frame, B., Frost, H. M., and Block, M. A.: Albright's hereditary osteodystrophy. Report of a family with studies of bone remodeling. *Ann. Intern. Med. 64:*996-1008, 1966.
38. Eyre, W. G., and Reed, W. B.: Albright's hereditary osteodystrophy with cutaneous bone formation. *Arch. Dermatol. 104:*632-42, 1971.
39. Walter, I. J. and McAlister, W. H.: Pseudohypoparathyroidism and myositis ossificans progressiva in the same patient. *J. Can. Assoc. Radiol. 23:*27-32, 1972.
40. Van Der Veen, E. A., Van Garsse, L. G. M. M., and Schreuder, H. B.: Pseudohypoparathyroidism and pseudopseudohypoparathyroidism in one family. *Neth. J. Med. 18:*262-68, 1975.
41. Steinbach, H. L. and Young, D. A.: The roentgen appearance of pseudohypoparathyroidism (PH) and pseudo-pseudo-hypoparathyroidism (PPH). *Am. J. Radiol.97:*49-66, 1966.
42. Jacobson, H. G., Rifkin, H., and Zucker-Franklin, D.: Werner's syndrome: A clinical-roentgen entity. *Radiology 74:*373-85, 1960.
43. Rosen, R. S., Cimini, R., and Coblentz, D.: Werner's syndrome. *Br. J. Radiol. 43:*193-198, 1970.
44. Goto, M., Horiuchi, Y., Tanimoto, K., Ishii, T., Nakashima, H.: Werner's syndrome: Analysis of 15 cases with a review of the Japanese literature. *J. Am. Geriatr. Soc. 26:*341-47, 1978.
45. Reeder, M. M.: Tropical diseases of the soft tissues. *Semin. Roetgenol. 8:*47-71. 1973.
46. Moskowitz, M.: Soft tissue changes accompanying vascular diseases of the extremities. *Semin. Roentgenol. 8:*91-100, 1973.
47. Lippmann, H. I. and Goldin, R. R.: Subcutaneous ossification of the legs in chronic venous insufficiency. *Radiology 74:*279-88, 1960.
48. Keats, T. E.: Post-injection calcification of the deltoid muscle. *Can. Assoc. Radiol. J. 29:*165-66, 1978.
49. Berger, P. E., Heidelberger, P., and Poznanski, A. K.: Extravasation of calcium gluconate as a cause of soft tissue calcification in infancy. *Am. J. Radiol. 121:*109-18, 1974.
50. Harris, V., Ramamurthy, R. S., and Pildes, R. S.: Late onset of subcutaneous calcifications after intravenous injections of calcium gluconate. *Am. J. Radiol. 123:*845-50, 1975.
51. McCandless, A. E.: Calcification and loss of subcutaneous tissue following trauma and hypothermia. *Arch. Dis. Childhood 26:*203-06, 1975.
52. Shackelford, G. D., Barton, L. L., and McAlister, W. H.: Calcified subcutaneous fat necrosis in infancy. *J. Can. Assoc. Radiol. 26:*203-06, 1975.
53. Beighton, P. and Horan, F.: Orthopaedic aspects of the Ehlers-Danlos syndrome. *J. Bone Joint Surg. 51B:*444-53, 1969.
54. Beighton, P. and Thomas, M. L.: The radiology of the Ehlers-Danlos syndrome. *Clin. Radiol. 20:*354-61, 1969.
55. Holt, J. F.: The Ehlers-Danlos syndrome. *Am. J. Radiol. 55:*420-26, 1946.
56. Shevick, M.: Pseudoxanthoma elasticum. *Angiology 22:*629-46, 1971.
57. James, A. E., Eaton, S. B. Blazek, J. V., et al.: Roentgen findings in pseudoxanthoma elasticum (PXE). *Am. J. Radiol. 106:*642-47.
58. Prick, J. J. and Thijssen, H. O. M.: Radiodiagnostic signs in pseudoxanthoma elasticum generalisatum (dysgenesis elastofibrillaris mineralisans). *Clin. Radiol 28:*549-54, 1977.
59. Smith, R.: Myositis ossificans progressiva: A review of current problems. *Semin. Arthritis Rheum. 4:*369-80, 1975.
60. Hentzer, B., Jacobsen, H. H., and Asboe-Hansen, G.: Fibrodysplasia ossificans progressiva. *Scand. J. Rheumatol. 6:*161-71, 1977.
61. Angervall, L., Stener, B., Stener, I., and Ahren, C.: Pseudomalignant osseous tumour of soft tissue. A clinical, radiological and pathological study of five cases. *J. Bone Joint Surg. 51B:*654-63, 1969.
62. Chaplin, D. M., and Harrison, M. H. M.: Pseudomalignant osseous tumour of soft tissue. Report of two cases. *J. Bone*

*Joint Surg. 54B:*334-40, 1972.
63. Goldman, A. B.: Myositis ossificans circumscripta: A benign lesion with a malignant differential diagnosis. *Am. J. Radiol. 126:*32-40, 1976.
64. Norman, A. and Dorfman, H. D.: Juxtacortical circumscribed myositis ossificans: Evolution and radiographic features. *Radiology 96:*301-06, 1970.
65. Goldberg, M. A. and Schumacher, H. R.: Heterotopic ossification mimicking acute arthritis after neurologic catastrophe. *Arch. Intern. Med. 137:*619-21, 1977.
66. Scher, A. T.: The incidence of ectopic bone formation in posttraumatic paraplegic patients of different racial groups. *Paraplegia 14:*202-06, 1976.
67. Money, R. A.: Ectopic paraarticular ossification after head injury. *Med. J. Aust. 1:*125-27, 1972.
68. Munster, A. M., Bruck, H. M., Johns, L. A., et al.: Heterotopic calcification following burns: A prospective study. *J. Trauma 12:*1071-74, 1973.